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Implications and Contribution: Children whose mothers experience anxiety and/or depression from pregnancy to child's age 6 years have an increased risk of developing chronic fatigue in early adolescence. Pediatricians treating children with CFS/ME should consider family-based approaches. Maternal mood disorders are potentially modifiable factors which merit further research in relation to pediatric CFS/ME.

ABSTRACT

Purpose: To investigate whether pre-morbid maternal and childhood psychological problems are risk factors for chronic disabling fatigue at age 13 years among children in the Avon Longitudinal Study of Parents & Children (ALSPAC) birth cohort.

Methods: Chronic disabling fatigue was defined as fatigue of at least 3 months, and up to 5 years, duration that prevented school attendance or hobbies/sport/leisure activities, and for which other causes were not identified. Maternal psychological factors were symptoms of anxiety and depression assessed up to 8 times between pregnancy and age 6 years. We investigated critical periods for maternal effects, and effects of paternal depression at 3 time-points. Child psychological factors included internalising and externalising problems and upsetting life events occurring at age 7-8 years.

Results: 110/5,657 children (1.9%) had chronic disabling fatigue at age 13 years. Maternal anxiety (adjusted odds ratio (AOR) 1.19 [95% CI 1.09-1.31] per episode), maternal depression (1.24 [1.11-1.39] per episode), child psychological problems (1.19 [1.00-1.41] per problem) and upsetting events (1.22 [0.99, 1.58] per event) were associated with chronic disabling fatigue. Associations of child psychological problems and upsetting events were attenuated (AOR=1.12 [0.93-1.33] per problem, AOR=1.19 [0.94, 1.52] per event) after further adjusting for maternal anxiety and depression.

Conclusions: Pediatricians need to be aware that children whose mothers experience anxiety and/or depression between pregnancy and child's age 6 years have an increased risk of developing chronic disabling fatigue in early adolescence. Conversely, clinicians need to be alert to fatigue in children whose mothers have longstanding anxiety and depression. These findings suggest the importance of family-based approaches to treatment.

Key words: pediatric fatigue, chronic fatigue syndrome, childhood adversity, maternal depression

Abbreviations:

ALSPAC	Avon Longitudinal Study of Parents and Children
CCEI	Crown-Crisp Experiential Index
CFS/ME	Chronic fatigue syndrome/myalgic encephalomyelitis
DAWBA	Development and Well-Being Assessment
EPDS	Edinburgh Postnatal Depression Scale
FAI	Family Adversity Index
IQR	Inter Quartile Range
NICE	National Institute for Health and Care Excellence
SDQ	Strengths and Difficulties Questionnaire
SMFQ	Short Moods and Feelings Questionnaire

INTRODUCTION

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is defined as fatigue lasting longer than three (1) or six (2) months and which "results in substantial reduction in previous levels of occupational, educational, social, or personal activities" (2) or "has resulted in a substantial reduction in activity level" (1). The estimated prevalence of CFS/ME in children ranges from 0.1% to 2.4%, with population surveys generating higher estimates (3-9) than studies in primary (10) or secondary care (11).

Anxiety and depression are common in children with CFS/ME (12-14), but it is unclear whether these are risk factors for, or consequences of, pediatric CFS/ME (15). Cohort studies have suggested that they are risk factors for chronic fatigue, but these studies were not sufficiently powered to investigate CFS/ME (9, 16-18). Mood disorders are common in mothers of children with CFS/ME who attend specialist services, but no study has explored whether this is a risk factor or secondary to their child's illness (19-21).

Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, we reported an association between family adversity and chronic disabling fatigue at age 13 years which suggested a particular effect of antenatal maternal psychopathology (5). We used the term "chronic disabling fatigue" as a proxy for CFS/ME, because children were not examined by a physician. Here we use data from the same cohort to investigate associations of maternal anxiety and depression from pregnancy to age 6 years, and childhood psychological problems and stressful life events at age 7-8 years, with chronic disabling fatigue at age 13 years. We used repeated measures of maternal anxiety and depression to investigate whether observed effects occurred at critical periods or as a result of accumulated exposure over time.

METHODS

Participants

ALSPAC is a population-based birth cohort designed to investigate a wide range of influences on the health and development of children (22). Pregnant women residing in the former Avon Health Authority in south-west England who had an estimated date of delivery between 1 April 1991 and 31 December 1992 were invited to take part, resulting in a cohort of 14,541 pregnancies and 13,978 children alive at 12 months of age (excluding triplets and quads). The primary source of data for the present study was parent-completed questionnaires administered at four time-points during the antenatal period then at regular intervals following birth. The ALSPAC study website contains details of all the data that are available through a fully searchable data dictionary (www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

Ethical approval

Ethical approval for this study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees.

Outcome (chronic disabling fatigue)

Our method for defining chronic disabling fatigue as a binary outcome has been described previously (5). We identified teenagers reported by their parent/carer to have "been feeling tired or lacking in energy" for "Between 3 and 5 months" or "Between 6 months and 5 years" and to have been absent from school "because of this tiredness or lack of energy" or for whom tiredness or lack of energy had "stopped him/her from playing, taking part in hobbies, sports or other leisure activities" "quite a lot" or "a great deal". We excluded children affected by fatigue for "More than 5 years" to prevent overlap with exposures occurring at age 7-8 years. We excluded those whose mothers thought that the fatigue was caused by playing too much sport, who had probable co-morbid depression (defined as a Short Moods and Feelings Questionnaire (SMFQ) score >10) (23) who snored often, or who had other illnesses that could cause fatigue (based on self-reported medication use).

Exposures

Maternal anxiety and depression

Mothers completed the Edinburgh Postnatal Depression Scale (EPDS) (24) and the Crown-Crisp Experiential Index (CCEI) (25) at 8 time-points: 18th and 32nd week of pregnancy, 8 weeks postpartum, and when the child was 8, 21, 33, 61, and 73 months old. EPDS scores were dichotomized at a cut-off of 12/13 to indicate probable depressive disorder (26). The CCEI comprises depression, anxiety and somatic symptoms sub-scales, which do not have standard cut-offs. We identified as having high levels of anxiety symptoms women who scored in the top 15% at each time-point.

Paternal depression

Fathers completed the EPDS at 8 time-points: 18th week of pregnancy and when the child was 8 and 21 months old. EPDS scores were dichotomized at a cut-off of 12/13.

Childhood psychological problems

Because DSM-IV psychiatric diagnoses have a very low prevalence among ALSPAC children aged 13 years and under, we defined 'childhood psychological problems' by dichotomising responses to individual symptom questions in the 'Development and Well-Being Assessment' (DAWBA, see www.dawba.com) self-report questionnaire from which DSM-IV diagnoses are derived (Table A1) (27). Symptoms are grouped according to the following psychological problems: separation anxiety; social fears; particular fears; general anxiety; sadness/depression; obsessions/compulsions; attention/activity problems; oppositional behaviour; and conduct problems. This questionnaire was completed by parents when children were approximately 7.5 (median 7.6, IQR 7.6 to 7.7) years old.

Upsetting events

'Upsetting Events' questions were completed by parents when children were approximately 8.5 (median 8.6, IQR 8.6 to 8.8) years old (Table A2), referring to events that had occurred since the child's 7th birthday and asking whether the child had been "very upset", "quite upset", "a bit

upset" or "wasn't upset" (if it had occurred). We included the following events: taken into care (state or foster care); physically hurt by someone; sexually abused; somebody in the family died; separated from mother; separated from father; changed care taker; separated from someone close; and lost best friend. These were scored dichotomously as having occurred (regardless of degree of upset) or not. We also included 'started a new school' if the mother reported that the child had been 'quite' or 'very' upset.

Strengths and Difficulties Questionnaire

The Strengths and Difficulties Questionnaire (SDQ), a behavioural screening questionnaire for 4-16 year-olds (28), was completed by the child's teacher at child age 8 (median 8.3, IQR 8.1 to 8.6) years as part of a questionnaire sent to primary schools during academic Year 3. The SDQ asks about 25 attributes, divided into 5 scales (emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and pro-social behaviour) each comprising 5 items. The five subscales are scored separately (see http://www.sdqinfo.com) on a scale from 0 - 10, and a 'total difficulties' score (from 0 - 40) is calculated as the sum of all subscales bar the pro-social. The teacher-completed SDQ has good internal consistency (Cronbach $\alpha \geq 0.7$) and test-retest reliability (≥ 0.65) for the sub-scale and total difficulties scores (29).

Family adversity index

The standard ALSPAC family adversity index (FAI) is derived from responses to questions asked during pregnancy about the following 10 factors, comprising 18 items in total: 1) age of mother at first pregnancy; 2) housing, comprising a) adequacy, b) basic amenities, c) defects, damp, infestation; 3) mother's and father's low educational attainment; 4) financial difficulties; 5) relationship with partner, comprising a) status, b) lack of affection, c) cruelty, d) lack of support; 6) family, comprising a) size, b) child in care, not with natural mother, or on at-risk register; 7) social network, comprising a) lack of emotional support, b) lack of practical support; 8) substance abuse; 9) crime, comprising a) being in trouble with the police and b) convictions; and 10) psychopathology of the mother (anxiety, depression or suicide attempts). Each of the 18 items is

assigned a value of 1 if an adversity is present and 0 if it is not present hence, the FAI has a range of 0 to 18. FAI scores are calculated where more than half of the items are valid, and non-adversity is assumed for any missing data hence, FAI scores are conservative (5). We excluded maternal psychopathology from the FAI because these were our primary exposures hence, our FAI had a range of 0 to 17.

Statistical analyses

We tested for differences between proportions and means using chi-squared tests and t-tests as appropriate. We used logistic regression to estimate crude and adjusted (for sex and family adversity) odds ratios for the association of each exposure with chronic disabling fatigue. To investigate possible dose-response associations we calculated the total number of episodes of anxiety and depression over the 8 time-points for mothers with complete data at all time-points, and the total number of psychological problems and upsetting events (allowing for up to 2 missing items, which were recoded as 'no problem' or 'no event'). For each exposure, we created a 4-level categorical variable coded as 0, 1 or 2, or 3+ episodes/problems/events. Maternal anxiety and depression were strongly positively correlated: correlation coefficients 0.74 – 0.77 between CCEI and EPDS scores measured at the same time-points. Therefore, in our final multivariable model, we averaged these exposures to avoid the inflated standard errors that occur when co-linear independent variables are included as separate independent variables. Missing data for maternal anxiety and depression, and child psychological problems, upsetting events and SDQ scores, were imputed from available data for these exposures and all other variables included in the models (including the outcome) using the chained equations approach to multiple imputation (30), combining parameter estimates using Rubin's rules (31). We investigated whether any effects of maternal anxiety and depression on fatigue in the child were best described by an accumulation of episodes or by episodes occurring during two critical periods: either antenatal (suggesting an *in utero* epigenetic event) or prior to the onset of disabling fatigue. The two time-points prior to the possible onset of fatigue were at ages 5 and 6 years) because the duration of fatigue was either 3-6

months or 6 months to 5 years. We compared regression models (in the complete and imputed datasets) following the method described by Mishra *et al* (32). Likelihood ratio tests were used to compare separate models containing terms for i) antenatal exposure only, ii) age 5-6 years exposure only, and iii) cumulative exposure (total number of time-points at which anxiety or depression occurred) with a 'saturated' model containing all of these terms plus an interaction term for antenatal × age 5-6 years exposure. P-values were inspected to determine whether any of these three models provide a fit as good as that for the saturated model. Small model P values provide evidence that the modelled effect alone does not sufficiently account for the overall association. All analyses were performed using Stata™.

RESULTS

Chronic disabling fatigue was identified in 117 children at age 13 years (5). We excluded 7 children affected by fatigue for >5 years (to prevent overlap with occurrence of exposures), leaving 110 children with fatigue lasting between 3 months and 5 years of whom 64 (58.2%) had been affected for 3-6 months and 46 (41.8%) had been affected for 6 months to 5 years (Figure 1). The questionnaire used to define fatigue was almost always completed by the mother alone (91.2% (5,088/5,576). The remainder was completed jointly by the mother and child (5.3% (293/5,576)), by the father alone (1.7% (93/5,576)) or by mothers and fathers jointly or with other people (1.8% (102/5576). The other questionnaires were also mainly completed by mothers alone: DAWBA 95% (3,354/3,510); upsetting events 97% (3,402/3,506).

Maternal anxiety data were available at all 8 time-points for 4,065 women, including the mothers of 88 children who had chronic disabling fatigue (Table A3). Maternal depression data were available at all 8 time-points for 4,226 women, including the mothers of 90 children who had chronic disabling fatigue. There were no differences in the availability of anxiety and depression data between children with and without chronic disabling fatigue. Complete DAWBA and upsetting event data were available for similar proportions (90-92%) of children with and without chronic disabling fatigue. SDQ data were available for 49.9% (2,746/5,499) of children without fatigue and for 48.2% (53/110) of children with chronic disabling fatigue.

Mothers of children with chronic disabling fatigue were slightly more likely to have experienced anxiety or depression during the 18th week of their pregnancy, and to have experienced a higher number of episodes of anxiety and depression from the 18th week of pregnancy until child's age 6 years (Table A3). Children with chronic disabling fatigue had a higher number of psychological problems at age 7 years, had experienced more upsetting events between ages 7 to 8 years, and had slightly higher SDQ scores at age 8 years.

<u>Maternal psychological factors</u>

The odds of chronic disabling fatigue at age 13 years increased with increasing episodes of maternal anxiety between pregnancy and child's age 6 years: odds ratio (OR) = 1.19 (95% CI 1.09 to 1.31) adjusted for sex and family adversity (Table 1). The OR (95% CI) comparing mothers who had 3+ episodes of anxiety with those who had none was 2.27 (1.32 to 3.91). The adjusted OR per episode of maternal depression between pregnancy and child's age 6 years was 1.24 (1.11 to 1.39), and the adjusted OR comparing children of mothers who had 3+ episodes of depression with those who had none was 2.61 (1.47 to 4.66). The adjusted OR per 0.5 episodes of maternal anxiety or depression was 1.24 (1.11 to 1.39). ORs were similar when missing data were imputed (Table 1).

When we looked at two *a priori* 'critical periods' (antenatal and child's age 5-6 years), the model containing only maternal anxiety when the child was 5-6 years old provided a fit equivalent to the fully-fitted ('saturated') model (Table A4). Thus, maternal anxiety at this age alone, rather than antenatal anxiety or both periods combined, described sufficiently the overall association of maternal anxiety with chronic disabling fatigue at age 13 years. By contrast, the model for an antenatal-only effect fitted less well than the saturated model. For maternal depression, there did not appear to be a critical period that explained the association of maternal depression with chronic disabling fatigue.

Paternal depression

Paternal depression data were available for 3,094 children, including 55 with chronic disabling fatigue. Chronic disabling fatigue was no more likely to occur among children of fathers who experienced 1+ episodes of depression at any of the three time-points (1.25% (2/160)) than among fathers who had none (1.81% (53/2,934)). The odds ratio for 1+ compared with 0 episodes, adjusted for child's sex and family adversity, was 0.61 (0.15 to 2.56).

Childhood psychological factors

Pre-morbid childhood psychological problems and upsetting events were associated with an increased risk of chronic disabling fatigue: OR=1.18 (1.02 to 1.37) per problem; OR=1.20 (0.97 to 1.48) per event (Table 2). The ORs comparing children for whom 3+ problems or 3+ events had occurred with those in who had experienced none were 2.03 (1.05 to 3.95) and 2.35 (1.04, 5.29), respectively. Associations of specific childhood psychological problems with chronic disabling fatigue are shown in Table A5. The effects of childhood psychological problems and upsetting events were attenuated when adjusted for maternal anxiety and depression: OR=1.12 (0.93 to 1.33) per psychological problem; OR=1.19 (0.94 to 1.51) per upsetting event. Effects were similar in analyses based on multiple imputations. The SDQ total difficulties score at age 8 years (rated by teachers) was not associated with chronic disabling fatigue (OR=1.03 (0.98 to 1.09) per unit score), and there was no consistent pattern in the ORs for the five SDQ subscales (Table A6).

DISCUSSION

This is the first study to show that maternal anxiety and depression are risk factors for pediatric chronic disabling fatigue. For maternal anxiety, exposure at age 5-6 years accounted for more of this association than did antenatal anxiety, whereas no critical period or cumulative effect could be discerned for maternal depression. Associations of childhood psychological problems and upsetting events with chronic disabling fatigue at age 13 years were attenuated after adjustment for maternal psychological factors.

Strengths and limitations

This study is, to our knowledge, the largest prospective population-based study to investigate pre-morbid maternal and childhood psychological factors associated with chronic disabling fatigue in adolescence. As is common in such studies, overall losses to follow-up were substantial - our analysis was based on observations from approximately 40% of the original cohort. However, the remaining sample was large, and we were able to investigate the effects of maternal anxiety and depression at multiple time-points in conjunction with childhood psychological symptoms and stressful life events. We used multiple imputations to correct for potential biases in our measures of effect due to losses to follow-up, which are known to be higher among participants from lower socioeconomic backgrounds (22). The similarity of estimates from raw and imputed datasets suggests that these differential losses to follow-up did not impart substantial bias.

We advise caution in extrapolating our findings to pediatric CFS/ME, for which our outcome can be considered a proxy. The main limitation of our outcome measure is that the definitions of chronic disabling fatigue at 13 were based on parental (mainly maternal) report. It is possible that mothers with depression or anxiety may over-report fatigue in their children. However, in a UK household survey, CFS/ME prevalence from parental report was lower (0.04%) than from interviews with children (0.2%) (3). As children were not examined by a physician, it is possible that we have included children with fatigue due to other causes. Although we believe this is

unlikely, because we excluded children on medication, children who snored, and children who were possibly depressed at age 13 years (5), we cannot discount this potential for misclassification. In excluding children with depression, we may have excluded those whose depression was co-morbid rather than primary, which would reduce the power in this study. Although we adjusted our final estimates for a family adversity index, which encompasses a range of confounders, it is likely that some residual confounding remains. We considered confounding factors for a particular risk factor to be those that were measured earlier than the risk factor, and that had potential effects on both the risk factor and the outcome. Thus, our estimates of the associations of child psychological problems and upsetting events (measured at ages 7-8 years) with chronic disabling fatigue were adjusted for episodes of maternal anxiety and depression (measured up to age 6 years). However, we did not adjust our estimates of the effects of maternal anxiety and depression for the later measures of child psychological problems and upsetting events, as these could not be confounding factors. For future research, we plan to conduct mediation analyses using repeated and contemporaneous measures of exposures and outcomes (disabling fatigue at older ages) from this cohort.

To investigate whether childhood psychological problems were associated with chronic disabling fatigue at age 13 years, we derived dichotomous variables to define children with the most severe symptoms, i.e. those reported to have suffered the symptoms the most often or a lot more than others of the same age. Although we do not know what the relationship is between these variables and actual DSM-IV diagnoses, or whether children who experience less severe symptoms are more likely to develop chronic disabling fatigue than children who experience no symptoms, our approach allowed us to investigate whether sub-threshold symptoms were associated with fatigue in this community sample of children.

Comparison with the literature

Whilst previous small cross-sectional studies have found that mothers of children with CFS/ME are more likely to have mood disorders (19-21), this is the first study to show that maternal mood disorders are present prior to, and increase the risk of, developing chronic disabling fatigue. We found that associations of childhood psychological problems with chronic disabling fatigue were confounded by maternal psychopathology. Although no previous studies have had sufficient power to explore risk factors with chronic disabling fatigue in children, our results are consistent with those that explored family disruption as a risk factor for functional somatic symptoms in adolescence (33). Too few ALSPAC participants had experienced sexual and physical abuse hence, we were unable to investigate whether the association between childhood abuse and CFS/ME in adults (34) could be replicated in this prospective cohort. However, early adversity in childhood (family adversity and upsetting life events) was a risk factor for pediatric chronic disabling fatigue in our cohort, which is consistent with retrospective studies in adults with CFS/ME.

We do not know why maternal anxiety and depression are risk factors for chronic disabling fatigue at 13 years of age. They could affect children's susceptibility to fatigue through *in utero* or early-life epigenetic or biochemical pathways (35, 36). However, our results suggest that the *in utero* period is not a critical period for either maternal anxiety or depression. Distress in the mother increases the likelihood of poorer family functioning and negative life events (37), which may increase stress for the child. Alternatively, maternal anxiety and depression may change childhood behaviors, for example, increasing or reducing physical exercise, which may be risk factors for chronic disabling fatigue (38, 39). Non-causal explanations include the possibility that anxiety or depression influenced mothers' responses to questionnaire items, or affected school attendance, which we used to identify children with chronic disabling fatigue. Inherited genetic variation linked with maternal psychopathology could play a role in susceptibility to fatigue in the child (40),

Conclusions

This is the first study to show that pre-morbid maternal anxiety and depression are risk factors for childhood CFS/ME. Although the underlying mechanisms are not known, pediatricians need to be aware that mothers of children with CFS/ME are more likely to have had long term problems with anxiety and depression, and they should consider family-based approaches to the treatment of pediatric CFS/ME. Conversely, clinicians need to be alert to early signs of disruptive fatigue in children whose mothers have longstanding anxiety and depression. In the meantime, further research is needed to elucidate possible pathways from anxiety and depression in mothers to chronic fatigue in children.

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Figure 1: Flow chart showing number of 13 year olds with fatigue, number excluded from analysis and number with disabling fatigue.

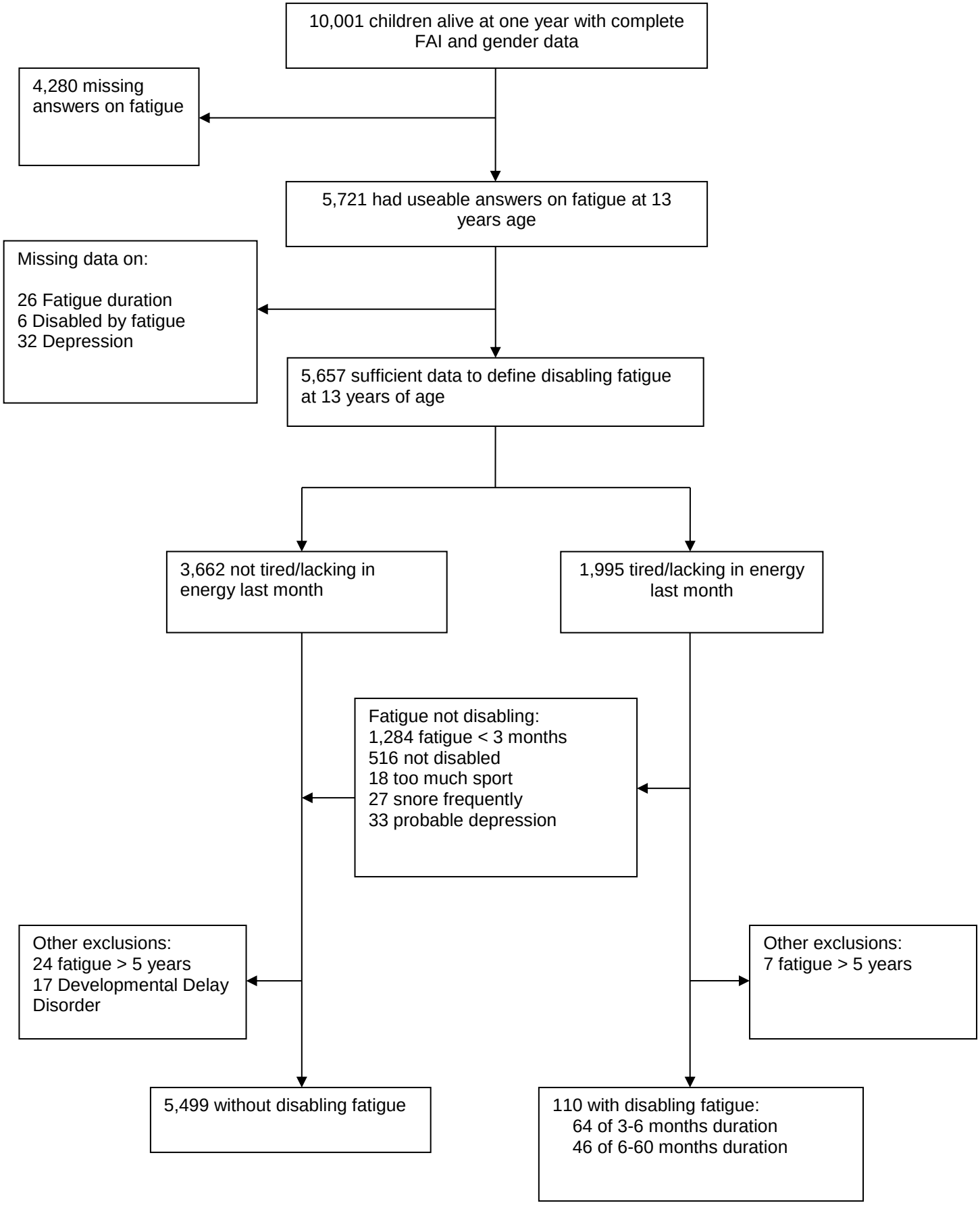

Table 1: Associations of number of episodes of maternal anxiety (Crown-Crisp Experiential Index score >8) and maternal depression (Edinburgh Depression Scale score >12) with chronic disabling fatigue at age 13 years in 3,866 children (83 with disabling fatigue) with complete anxiety and depression data (5,609 children for analyses based on multiple imputation).

	Fatigued/Total (%)	Crude odds ratio (95% CI)	Odds ratio adjusted for sex and family adversity index (95% CI)
Total episodes of maternal anxiety			
0	37/2,379 (1.6%)	1.00 (reference)	1.00 (reference)
1 or 2	22/861 (2.6%)	1.66 (0.97, 2.83)	1.59 (0.93, 2.72)
3+	24/626 (3.8%)	2.52 (1.50, 4.25)	2.27 (1.32, 3.91)
Per episode of maternal anxiety		1.22 (1.11, 1.33), P<0.001	1.19 (1.09, 1.31), P<0.001
Per episode of maternal anxiety (analysis using multiple imputation)[a]		1.19 (1.10, 1.28), P<0.001	1.17 (1.08, 1.28), P<0.001
Total episodes of maternal depression			
0	44/2,639 (1.7%)	1.00 (reference)	1.00 (reference)
1 or 2	20/827 (2.4%)	1.46 (0.86, 2.49)	1.40 (0.81, 2.39)
3+	19/400 (4.8%)	2.94 (1.70, 5.09)	2.61 (1.47, 4.66)
Per episode of maternal depression		1.27 (1.14, 1.41), P<0.001	1.24 (1.11, 1.39), P<0.001
Per episode of maternal depression (analysis using multiple imputation)[a]		1.23 (1.12, 1.35), P<0.001	1.21 (1.10, 1.33), P<0.001
Average of episodes of maternal anxiety or depression			
0	33/2,159 (1.5%)	1.00 (reference)	1.00 (reference)
0.5 – 1.0	18/819 (2.2%)	1.45 (0.81, 2.59)	1.38 (0.77, 2.48)
1.5+	32/888 (3.6%)	2.41 (1.47, 3.94)	2.19 (1.31, 3.65)
Per 0.5 episodes of maternal anxiety or depression		1.27 (1.15, 1.40), P<0.001	1.24 (1.11, 1.39), P<0.001
Per 0.5 episodes of maternal anxiety or depression (analysis using multiple imputation)[a]		1.23 (1.13, 1.34), P<0.001	1.21 (1.11, 1.34), P<0.001

[a] Based on data from 5,609 children (110 with disabling fatigue) with imputation using available episodes of maternal anxiety and depression, and childhood psychological problems, upsetting events, and SDQ scores

Table 2: Associations of child psychological problems at age 7 years and upsetting events between age 7-8 years with chronic disabling fatigue at age 13 years.

		Analyses in 4,758 children (95 with disabling fatigue) with no more than 2 missing items for psychological problems or upsetting events		Analyses restricted to 3,513 children (73 with disabling fatigue) with complete maternal anxiety and depression data and no more than 2 missing items for psychological problems or upsetting events	
Psychological problem	Fatigued/Total (%)	Crude odds ratio (95% CI)	Odds ratio adjusted for sex and family adversity index (95% CI)	Odds ratio adjusted for sex and family adversity index (95% CI)	Odds ratio additionally adjusted for episodes of maternal anxiety and depression (95% CI)
Total psychological problems					
0	41/2,797 (1.5%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1 or 2	42/1,582 (2.7%)	1.83 (1.19, 2.83)	1.78 (1.15, 2.75)	2.16 (1.31, 3.55)	2.00 (1.21, 3.31)
3+	12/379 (3.2%)	2.20 (1.14, 4.22)	2.03 (1.05, 3.95)	1.96 (0.88, 4.40)	1.56 (0.68, 3.58)
Per psychological problem		1.21 (1.04, 1.40), P=0.01	1.18 (1.02, 1.37), P=0.03	1.19 (1.00, 1.41), P=0.05	1.12 (0.93, 1.33), P=0.23
Per psychological problem (analysis using multiple imputation)[a]		1.17 (1.02, 1.35), P=0.02	1.14 (0.99, 1.32), P=0.07	1.14 (0.99, 1.32), P=0.07	1.09 (0.94, 1.26), P=0.27
Total upsetting events					
0	46/2,820 (1.6%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1 or 2	42/1,761 (2.4%)	1.47 (0.97, 2.25)	1.45 (0.95, 2.22)	1.49 (0.92, 2.42)	1.44 (0.88, 2.34)
3+	7/177 (4.0%)	2.48 (1.10, 5.58)	2.35 (1.04, 5.29)	2.82 (1.16, 6.88)	2.36 (0.96, 5.81)
Per upsetting event		1.22 (0.99, 1.50), P=0.06	1.20 (0.97, 1.48), P=0.09	1.25 (0.99, 1.58), P=0.06	1.19 (0.94, 1.52), P=0.14
Per upsetting event (analysis using multiple imputation)[a]		1.26 (1.04, 1.52), P=0.02	1.23 (1.01, 1.49), P=0.04	1.23 (1.01, 1.49), P=0.04	1.19 (0.98, 1.44), P=0.08

[a]Based on data from 5,609 children (110 with disabling fatigue) with imputation using available episodes of maternal anxiety and depression, and childhood psychological problems, upsetting events, and SDQ score

APPENDICES

Table A1. Prevalence in the ALSPAC cohort of DSM-IV disorders and psychological problems derived from the 'Development and Well-Being Assessment' (DAWBA) questionnaire at age 7 years

DSM-IV diagnosis		'Childhood psychological problem' derived for current study		
Disorder derived from DAWBA	Prevalence in ALSPAC study population	Outcome variables derived from DAWBA	Derivation of dichotomous outcome variables from list of symptoms in DAWBA and examples of items in DAWBA relating to each outcome	Prevalence in ALSPAC study population
Separation anxiety	0.8%	Separation anxiety	Any separation anxiety symptom(s) 'a lot more than others' compared to 'no more than others' or 'a little more than others' e.g. has he/she worried about sleeping alone?	7.2%
Social phobia	0.3%	Social fears	Any social fears 'a lot' compared to 'none', 'a lttle', or 'hasn't done this in the last month' e.g. has he/she been afraid of meeting new people?	5.5%
Specific phobia	1.1%	Particular fears	Any particular fears 'a great deal' compared to 'quite a lot', 'only a little' or 'not at all' e.g. is he/she scared of the dark?	12.4%
Generalized anxiety disorder	0.5%	General anxiety	Any of the worries 'often' compared to 'sometimes' or 'not at all' e.g. does he/she worry a lot about schoolwork, homework or tests/examinations?	8.5%
Any depressive disorder	0.5%	Sadness/ depression	Any mood symptoms compared to none e.g. did he/she think about death a lot?	11.8%
Obsessive-compulsive disorder	0.1%	Obsessions/ compulsions	Any of the behaviours 'sometimes' or 'often' compared to 'none' e.g checking things (doors, ovens, locks, etc), excessive cleaning (handwashing, toothbrushing, etc).	7.8%
Any ADHD disorder	2.1%	Attention & activity problems	Any attention/activity problems 'a lot more than others' compared to 'a little more than others' or 'none' e.g. does he/she often fidget? Is he/she easily distracted?	14.6%
Oppositional-defiant disorder	2.1%	Oppositional behaviour	Any of the behaviours 'a lot more than others' compared to 'no more than others' or 'a little more than others' e.g. has he/she had severe temper tantrums?	6.2%
Conduct disorder	0.6%	Conduct problems	Any of the behaviours 'definitely/often/ more than once' compared to 'none', or 'perhaps' / 'sometimes'/ 'once only' e.g. has he/she bullied or threatened people?	6.6%

Table A2: ALSPAC upsetting events questionnaire (for children age 8 years)

Below are listed some events that might upset some children. Please state whether any of these has happened since he was 7 years old.	Included in our analysis (y/n)
E1. He was taken into care	y
E2. A pet died	n
E3. He moved home	n
E4. He had a shock or fright*	n
E5. He was physically hurt by someone	y
E6. He was sexually abused	y
E7. Somebody in the family died	y
E8. He was separated from his mother	y
E9. He was separated from his father	y
E10. He acquired a new mother or father	n
E11. He had a new brother or sister	n
E12. He was admitted to hospital	n
E13. He changed care taker (i.e. the person mostly looking after him)	y
E14. He was separated from someone else that he was close to	y
E15. He started a new school	y
E16. He lost his best friend	y

Table A3: Mean (SD) or frequency (%) for maternal and child characteristics and data availability, comparing children with and without chronic disabling fatigue at age 13 years

		With chronic disabling fatigue (n=110 unless otherwise indicated)	Without chronic disabling fatigue (n=5,499 unless otherwise indicated)
Male sex		54 (49.1%)	2,772 (50.4%)
Family adversity index (range 0 – 13)		1.01 (1.32)	0.76 (1.17)
Crown-Crisp Experiential Index (CCEI) score at 18 wks gestation (range 0 – 16)		5.69 (3.4), n=108	4.57 (3.35), n=5,409
Maternal anxiety (CCEI score > 8) at 18 wks gestation		21 (19.4%), n=108	724 (13.4%), n=5,409
Number of time points for which maternal anxiety data were available from pregnancy to age 6 years (range 0 – 8)	8	88 (80.0%)	3,977 (72.3%)
	7	17 (15.5%)	895 (16.3%)
	6	3 (2.7%)	362 (6.6%)
	≤5	2 (1.8%)	265 (4.8%)
Number of episodes of anxiety (CCEI score > 8) (range 0 – 8)		1.98 (2.51)	1.06 (1.82)
Edinburgh Depression Scale (EPDS) score at 18 wks gestation (range 0 – 30)		7.84 (5.15), n=109	6.32 (4.53), n=5,442
Maternal depression (EPDS score > 12) at 18 wks gestation		17 (15.6%), n=109	565 (10.4%), n=5,442
Number of time points for which maternal depression data were available from pregnancy to age 6 years (range 0 – 8)	8	90 (81.8%)	4,136 (75.2%)
	7	14 (12.7%)	796 (14.5%)
	6	5 (4.6%)	319 (5.8%)
	≤5	1 (0.9%)	248 (4.5%)
Number of episodes of depression (EPDS score > 12) (range 0 – 8)		1.33 (2.08)	0.72 (1.40)
Data available for psychological problems at age 8 years		101 (91.8%)	4,998 (90.9%)
Psychological problems at age 8 years (range 0 – 9)		1.45 (1.48)	1.14 (1.36)
Data available for upsetting events between ages 7-8 years		100 (90.9%)	4,947 (90.0%)
Upsetting events between ages 7-8 years (range 0 – 10)		0.78 (0.85)	0.57 (0.84)
SDQ data available at age 8 years		53 (48.2%)	2,746 (49.9%)
SDQ total difficulties score at age 8 years (range 0 – 40)		5.96 (5.92)	4.59 (5.41)

Table A4: P values comparing models for early, late, and cumulative effects of maternal anxiety and depression on chronic disabling fatigue at age 13 years

		Complete data analysis[a]	Imputed data analysis[b]
	Model	P-value[c]	P-value[c]
Anxiety	Saturated	1.00	1.00
	No effect	0.001	0.001
	Antenatal	0.001	0.001
	Age 5-6 years	0.50	0.54
	Cumulative	0.24	0.15
Depression	Saturated	1.00	1.00
	No effect	0.31	0.30
	Antenatal	0.59	0.45
	Age 5-6 years	0.44	0.54
	Cumulative	0.79	0.69

[a] Based on data from 3,570 children (76 with disabling fatigue) with complete anxiety and depression data

[b] Based on data from 5,609 children (110 with disabling fatigue), with imputation using all available episodes of maternal anxiety and depression, and childhood psychological problems, upsetting events, and SDQ scores

[c] P-values derived from likelihood ratio tests comparing models containing terms for i) antenatal exposure only (18^{th} and 32^{nd} week of pregnancy), ii) childhood exposure only (age 5 to 6 years), and iii) cumulative exposure (antenatal plus childhood occurrences) with a 'saturated' (reference) model containing all of these terms plus an interaction term for early × late exposure: large P-value indicates that the model provides a fit which is as good as that obtained in the saturated model; small P-value indicates that the model is not supported by the data

Table A5: Psychological problems at age 7 years, upsetting events between ages 7-8 years and chronic disabling fatigue at age 13 years

			Odds ratio (95% CI) for association with disabling fatigue at age 13	
	Fatigued	Not fatigued	Crude	Adjusted for sex and family adversity index
Psychological problem*	n=94	n=4,686		
Separation anxiety	7 (7.5%)	291 (6.2%)	1.22 (0.56, 2.65)	1.13 (0.52, 2.47)
Social fears	7 (7.5%)	228 (4.9%)	1.57 (0.72, 3.44)	1.54 (0.70, 3.36)
Particular fears	14 (14.9%)	552 (11.8%)	1.31 (0.74, 2.33)	1.26 (0.71, 2.24)
General anxiety	11 (11.7%)	368 (7.9%)	1.56 (0.82, 2.94)	1.51 (0.80, 2.87)
Sadness/depression	14 (14.9%)	536 (11.4%)	1.35 (0.76, 2.41)	1.31 (0.73, 2.33)
Obsessions/compulsions	9 (9.6%)	389 (8.3%)	1.17 (0.58, 2.34)	1.12 (0.56, 2.26)
Attention & activity problems	13 (13.8%)	450 (9.6%)	1.51 (0.83, 2.74)	1.39 (0.76, 2.54)
Oppositional behaviour	10 (10.6%)	238 (5.1%)	2.22 (1.14, 4.34)	2.05 (1.04, 4.05)
Conduct problems	8 (8.5%)	262 (5.6%)	1.57 (0.75, 3.28)	1.43 (0.68, 3.01)
Upsetting event**	n=98	n=4,858		
Taken into care (state or foster)	0 (0.0%)	1 (<0.1%)	-	-
Physically hurt by someone	4 (4.1%)	165 (3.4%)	1.21 (0.44, 3.33)	1.13 (0.41, 3.13)
Sexually abused	0 (0.0%)	4 (0.1%)	-	-
Somebody in the family died	29 (29.6%)	1,102 (22.7%)	1.43 (0.92, 2.22)	1.43 (0.92, 2.22)
Separated from mother	1 (1.0%)	126 (2.6%)	0.39 (0.05, 2.80)	0.36 (0.05, 2.62)
Separated from father	7 (7.1%)	289 (6.0%)	1.22 (0.56, 2.65)	1.11 (0.51, 2.44)
Changed care taker	3 (3.1%)	99 (2.0%)	1.52 (0.47, 4.87)	1.46 (0.45, 4.69)
Separated from someone close	6 (6.1%)	191 (3.9%)	1.59 (0.69, 3.69)	1.47 (0.63, 3.42)
Started a new school (and was upset)	12 (12.2%)	317 (6.5%)	2.00 (1.08, 3.70)	1.95 (1.05, 3.62)
Lost best friend	12 (12.2%)	447 (9.2%)	1.38 (0.75, 2.54)	1.36 (0.74, 2.51)

* Based on data from 4,780 children (94 with disabling fatigue) with complete psychological problem data

** Based on data from 4,956 children (98 with disabling fatigue) with complete upsetting event data

Table A6. Strengths and Difficulties Questionnaire (SDQ) scores at age 8 years (School Year 3, questionnaire completed by child's teacher) and chronic disabling fatigue at age 13 years

	Fatigued (n=50)	Not fatigued (n=2,612)	Odds ratio (95% CI) for association with disabling fatigue at age 13 years		
	Mean (SD) score	Mean (SD) score	Crude	Adjusted for sex and family adversity index	Imputed data analysis, adjusted for sex and family adversity index*
Pro-social	7.4 (2.5)	8.0 (2.3)	0.91 (0.81, 1.02)	0.91 (0.81, 1.03)	0.95 (0.85, 1.07)
Hyperactivity	2.4 (2.7)	2.2 (2.4)	1.04 (0.94, 1.17)	1.03 (0.92, 1.15)	1.00 (0.92, 1.10)
Emotional symptoms	1.9 (2.1)	1.2 (1.8)	1.16 (1.03, 1.32)	1.16 (1.02, 1.31)	1.06 (0.91, 1.22)
Conduct problems	0.5 (1.2)	0.5 (1.1)	1.00 (0.78, 1.28)	0.97 (0.75, 1.25)	0.95 (0.74, 1.21)
Peer problems	1.1 (1.5)	1.0 (1.6)	1.04 (0.88, 1.22)	1.02 (0.87, 1.21)	1.01 (0.87, 1.16)
Total difficulties	5.9 (5.4)	4.9 (4.9)	1.04 (0.99, 1.09)	1.03 (0.98, 1.09)	1.01 (0.97, 1.05)

* Based on data from 5,609 children (110 with disabling fatigue) with imputation using available episodes of maternal anxiety and depression, and childhood psychological problems, upsetting events, and SDQ scores